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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/965,825	DUSCH ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/1/2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/5/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 32-58 are pending.

Applicant's cancellation of claims 1-31, addition of claims 32-58, submission of foreign documents GERMANY 100 48 604.5 filed on 09/30/2000, and GERMANY 101 17 085.8 filed on 04/06/2001, and English translations of the foreign documents, in a communication filed 4/5/2004 are acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 4/5/2004 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

2. Claim 51 is objected to due to the recitation of "patothenate". It is suggested that the term be replaced with "pantothenate". Appropriate correction is required.

3. Claim 56 is objected to due to the recitation of "selected from the group consisting of the complement of.....and complement of SEQ ID NO: 4 and which encodes a protein...". For clarity, it is suggested that a comma be inserted between " SEQ ID NO: 4" and the term "and which encodes..." to clearly indicate that the term "which encodes..." is not part of "the group consisting of". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 56 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 56 is indefinite in the recitation of "complement of SEQ ID NO: #" because it is unclear which "complements" are encompassed by the claims. Fragments of any size which are complementary to the polynucleotides claimed can be considered as "complements". Applicants have not define the term "complement", as it relates to size, in the specification either. If Applicant's intended complement is the entire complement, it is suggested that the term "complement" be replaced with "complete complement". For examination purposes, the suggested language will be used. Correction is required.

7. Claims 57 and 58 are indefinite in the recitation of "the process of claim 56, wherein said poxB gene comprises SEQ ID NO: 1" for the following reasons. Claim 56, from which claims 57-58 depend, recites "wherein said poxB gene.....encodes a protein having reduced pyruvate oxidase activity compared to a protein encoded by SEQ ID NO: 1". Thus, it is unclear how the poxB gene can comprise SEQ ID NO: 1 or SEQ ID NO: 4 if both SEQ ID NO: 1 and SEQ ID NO: 4 encode the same wild-type poxB gene product and claim 56 recites a limitation indicating that the poxB gene should encode a protein with reduced pyruvate oxidase activity compared to that encoded by the polynucleotide of SEQ ID NO: 1. It is noted that SEQ ID NO: 4 (3248 nucleotides) comprises SEQ ID NO: 1 (2160 nucleotides), which in turn comprises the entire coding region. For examination purposes, no patentable weight will be given to claims 57-58 and they will be considered duplicates of claim 56. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

9. Newly added claims 35-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 35-39 are directed to a process for preparing D-pantothenic acid by culturing a recombinant Coryneform bacterium wherein said bacterium expresses a reduced level of the poxB gene product, and wherein the expression of the poxB gene product is reduced at least 5%, 10%, 25%, 50% or 75% compared to an unmodified Coryneform bacterium. While the Examiner has found support for expression of a poxB gene product (pyruvate oxidase) wherein the activity of said gene product is reduced at least 5%, 10%, 25%, 50% or 75% compared to that found in an unmodified Coryneform bacterium (paragraphs 29 and 66 of U.S. Publication No. 20020150999), the Examiner is unable to find support for expression of the poxB gene product which is reduced at least 5%, 10%, 25%, 50% or 75% compared to an unmodified Coryneform bacterium. Thus there is no indication that a process for preparing D-pantothenic acid by culturing a recombinant Coryneform bacterium wherein said bacterium expresses a reduced level of the poxB gene product, and wherein the expression of the poxB gene product is reduced at least 5%, 10%, 25%, 50% or 75% compared to an unmodified Coryneform bacterium was within the scope of the invention as conceived by Applicants at the time the application was filed. Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

10. Claims 32-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length regarding claims 1, 5-12, 18 and 31. It is now applied to newly added claims 32-58 for the reasons of record and those set forth below.

11. Applicants argue that a written description rejection would not apply to new claims 32-58 and direct the Examiner's attention to specific sections of the specification in support of the argument that the claimed invention is adequately described.

12. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. Claims 32, 33, 40, 46-50, 53-58 are directed to a process for preparing D-pantothenic acid by cultivating a genus of Coryneform bacteria which has been modified in any way such that (a) said bacteria express a reduced level of the poxB gene product, or (b) said bacteria produce a pyruvate oxidase with reduced activity compared to the pyruvate oxidase activity found in unmodified Coryneform bacteria. It is noted that while claims 56-58 define the structure of the poxB gene in the Coryneform bacteria, the claims still require a genus of Coryneform bacteria modified as indicated above in (a) and (b). Claim 34 is directed to the process of claim 33 as described above with the added limitation that the poxB gene product is eliminated in any way. Claims 35-39 are directed to the process described above with the added limitation that the expression of the poxB gene product is reduced at least 5%, 10%, 25%, 50% or 75% compared to an unmodified Coryneform bacterium. Claims 41-45 are directed to the process described above with the added limitation that the activity of the poxB gene product, which is pyruvate oxidase, is reduced by at least 5%, 10%, 25%, 50% or 75% of that found in an unmodified Coryneform bacterium. Claim 51 is directed to the process described above regarding claim 32 with the added limitation that the genus of Coryneform bacteria is further modified in any way such that said bacteria

comprises increased amounts of the panB, ilvC and/or ilvD gene products. Claim 52 is directed to the process of claim 52 with the added limitation that the panB, ilvC and/or ilvD genes in the genus of Coryneform bacteria are overexpressed.

While the specification discloses the C. glutamicum poxB gene and a method to produce D-pantothenic acid in C. glutamicum by inactivating the C. glutamicum poxB gene wherein said inactivation occurs by homologous recombination such that a deletion in the poxB gene is obtained, the specification is completely silent regarding (1) the structures of other poxB, panB, ilvC and ilvD genes from other Coryneform bacteria, (2) other methods to reduce expression of any poxB gene from Coryneform bacteria such as modifications in the regulatory region of the poxB gene, (3) how to reduce expression of any poxB gene from Coryneform bacteria by at least 5%, 10%, 25%, 50% or 75% compared to an unmodified Coryneform bacteria, (4) other methods to reduce activity of the poxB gene product of any Coryneform bacteria such as inhibitors of pyruvate oxidase activity or structural modifications in any poxB gene from any Coryneform bacteria that would result in a pyruvate oxidase with reduced activity compared to the wild-type pyruvate oxidase activity, (5) how to reduce pyruvate oxidase activity by at least 5%, 10%, 25%, 50% or 75% compared to an unmodified Coryneform bacteria, (6) other methods to eliminate pyruvate oxidase activity in addition to deletions in the poxB gene, such as inhibitors, or (7) methods to increase the amounts of the panB, ilvC and/or ilvD gene products from any Coryneform bacteria in addition to overexpression of said genes via a strong promoter, such as by modifying the regulatory regions.

The claimed method requires a genus of Coryneform bacteria genes which has not been adequately described as their structures have not been disclosed, with the exception of SEQ ID NO: 4 (SEQ ID NO: 1 and 3 are fragments of SEQ ID NO: 4). While a sufficient written description of a genus of DNAs may be achieved by a recitation of a representative number of DNAs defined by a nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute

a substantial portion of the genus, in the instant case, most of the claims do not recite a structural limitation in regard to the poxB gene and none of the claims recite a structural limitation regarding the panB, ilvC or the ilvD genes. As indicated previously, the art as evidenced particularly by Witkowski et al., Seffernick et al. and Broun et al. clearly indicate the unpredictability of accurately determining function based solely on structural homology. Therefore, the genus of genes required to practice the claimed method has the potentiality of encompassing structurally diverse species which cannot be adequately described by a single structure, i.e. SEQ ID NO: 1. Furthermore, the claimed method requires a genus of modifications which are unknown. Thus, in view of the information provided, one cannot reasonably conclude that the claimed invention is adequately described.

13. Claims 32-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for the production of D-pantothenic acid in C. glutamicum by inactivating the C. glutamicum poxB gene wherein said inactivation occurs by a deletion in the poxB gene, and a process as described above wherein at least one of the C. glutamicum panB, C. glutamicum panC, C. glutamicum panD, or C. glutamicum ilvD genes are over expressed by using a strong promoter, does not reasonably provide enablement for (1) a process for preparing D-pantothenic acid by cultivating any Coryneform bacteria which has been modified in any way such that (a) said bacteria express a reduced level of the poxB gene product, or (b) said bacteria produce a pyruvate oxidase with reduced activity compared to the pyruvate oxidase activity found in unmodified Coryneform bacteria (2) the process of (1) with the added limitation that the poxB gene product is eliminated in any way, (3) the process of (1) with the added limitation that the expression of the poxB gene product is reduced by at least 5%, 10%, 25%, 50% or 75% compared to an unmodified Coryneform bacterium, (4) the process of (1) with the added limitation that the activity of the poxB gene product is reduced by at least 5%, 10%, 25%, 50% or 75% of that found in an unmodified Coryneform bacterium, (5) the process of (1) with the added limitation that

the Coryneform bacteria are further modified in any way such that said bacteria comprises increased amounts of the panB, ilvC and/or ilvD gene products, or (6) the process of (1) with the added limitation that the panB, ilvC and/or ilvD genes in the Coryneform bacteria are overexpressed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length regarding claims 1, 5-12, 18 and 31. It is now applied to newly added claims 32-58 for the reasons of record and those set forth below.

14. Applicants argue that an scope of enablement rejection would not apply to new claims 32-58 and direct the Examiner's attention to specific sections of the specification in support of the argument that the claimed invention is enabled by the specification.

15. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. The scope of the claims, already described above, is not commensurate with the enablement provided in view of the large number of unknown poxB, panB, ilvC and ilvD gene structures as well as the large number of unknown modifications required to practice the claimed method. The specification as discussed above is completely silent in regard to the structures of all the genes required, all the modifications required to express a reduced level of the poxB gene product, all the modifications required to produce an increase in the synthesis panB, ilvC and ilvD gene products, inhibitors of pyruvate oxidase activity, how to obtain the specific reduction levels recited in regard to expression of the poxB gene, how to produce a poxB gene product with less activity as recited, how to eliminate pyruvate oxidase activity in addition to deletions to the poxB gene, and how to increase the amount of panB, ilvC and ilvD gene products in addition to overexpression of said genes by using a strong promoter. Furthermore, the art teaches the unpredictability of the art in regard to isolating structural homologs having the same function based solely on structural homology. Therefore, in view of the information provided, the lack of knowledge about the modifications and gene structures required to practice the claimed method, the

unpredictability of the art regarding the isolation of functional homologs based solely on structural homology, one of skill in the art cannot reasonably conclude that the full scope of the claims is enabled by the specification.

Conclusion

16. No claim is in condition for allowance.

17. Applicant's amendment canceling claims 1-31 and adding new claims 32-58 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

19. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
June 10, 2004

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1600